Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

Session 4

1. Topic and Author

Selective Estrogen Receptor Modulators and Cardiovascular Disease
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Selective Estrogen Receptor Modulators (SERMs) are non-hormonal agents that bind with high affinity to estrogen receptors and may exhibit either estrogen agonistic or antagonistic effects depending on the target tissue. SERMs, such as tamoxifen and raloxifene, share many biological effects on the cardiovascular system in common with hormone replacement therapy (HRT), but also have potentially important differences. Unlike HRT, SERMs do not increase high density lipoprotein (HDL) cholesterol or triglycerides, and do not increase C-reactive protein. Several beneficial effects of SERMs on surrogate markers of cardiovascular disease (CVD) have been demonstrated including: reductions in low density lipoprotein (LDL) cholesterol, apolipoprotein B, lipoprotein (a), fibrinogen, and homocysteine. Endothelia dysfunction, an early indicator of atherosclerosis, is improved in some studies with SERMs, but not in others. Inflammatory mediators may contribute to endothelial dysfunction by increasing the expression of vascular adhesion molecules, such as E selectin and intracellular adhesion molecule (ICAM-1), both of which are reduced by HRT and SERMs. In contrast vascular cell adhesion molecule (VCAM-1) is reduced by HRT but not by SERMs, and the expression of matrix metalloproteinases (MMP) is increased by HRT but not by SERMs. In cynomologus monkeys tamoxifen and estrogen have been shown to slow the progression of atherosclerosis, whereas raloxifene did not. Preliminary cardiovascular endpoint data on tamoxifen has been mixed, and in an osteoporosis outcomes trial, raloxifene was associated with a reduction in cardiovascular events among women at high risk of such events. There are no completed clinical outcomes studies of SERMs with an a priori primary outcome of CVD. The Raloxifene Use for the Heart (RUTH) Study is a double blind, placebo controlled clinical trial currently underway in 10,101 women at high risk of cardiovascular events from 26 countries. There are 2 primary endpoints including invasive breast cancer and cardiovascular disease (hospitalized acute coronary syndromes, non-fatal myocardial infarction and coronary death). Several secondary endpoints will also be evaluated.

3. Current challenges and the most important issues for future research

It is not known if differential effects of SERMs and HRT on surrogate markers of atherosclerosis will translate into significant differences in clinical outcomes. Future research should focus on determining the net benefit of SERMs on chronic diseases in postmenopausal women with a diverse range of risk.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

There is tremendous confusion about the role of HRT in CVD, and this has also raised questions and concerns about the potential risks and benefits of SERMs for CVD. Much of the public and medical profession is not familiar with the differences between SERMs and HRT. Although there are differential effects on surrogate markers of CVD, we need to be clear that the clinical impact of SERMs can only be determined in well designed clinical trials and that the results of the recent HRT trials may or may not be predictive of SERM trials.

5. Translating new findings to improved diagnosis and treatment/saving lives.

Results of ongoing trials of SERMs on cardiovascular endpoints will help define the role of SERMs in reducing the incidence of the leading killer of postmenopausal women. Data from recent studies are promising but are not sufficient to formulate clinical recommendations regarding the use of SERMs for the prevention of CVD.

6. References.

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